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COMPARISON OF UNRELATED CORD BLOOD TRANSPLANTATION AND HUMAN LEUCOCYTE ANTIGEN MISMATCHED UNRELATED BONE MARROW TRANSPLANTATION FOR ADULT PATIENTS WITH HEMATOLOGICAL MALIGNANCY

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First recommended alternative donor to human-leucocyte antigen (HLA) matched sibling for hematopoietic stem cell transplantation (HSCT) is HLA 8/8 allele matched unrelated donor. There still are a number of patients who need to find second alternative donor. Recent advances in unrelated cord blood transplantation (UCBT) enabled patients to increase the choices for second alternative donor/stem cell source.

We made a HLA mismatched-locus-specific comparison of the outcomes of unrelated cord blood and bone marrow recipients. 1196 HLA one or two high resolution mismatched (class I one-allele mismatched, 491, class II one-allele mismatched, 314, two-allele mismatched, 391) BM recipients and 418 HLA-A, -B high resolution, and –DRB1 low resolution zero to two antigen mismatched (matched, 25, one-antigen mismatched, 105, two-antigen mismatched, 288) CB recipients were analyzed. Subjects were limited to adult patients whose age was 16 years or older at the time of transplant who received first stem cell transplantation with myeloablative conditioning for hematological malignancy.

With adjusted analyses, HLA one- (relative risk [RR] = 1.00, 95% confidence interval [CI], 0.73-1.37, P = 0.99) or two- (HR = 0.97, 95%CI, 0.76-1.22, P = 0.77) antigen mismatched UCBT and HLA-C one-allele mismatched UBMT (RR = 0.96, 95%CI, 0.77-1.20, P = 0.74) showed similar overall mortality compared to HLA-DRB1 one-allele mismatched UBMT. UCBT showed higher relapse rate (RR = 2.47 for matched, RR = 1.93 for one-antigen mismatched, RR = 1.53 for two-antigen mismatched, P = 0.013, 0.0051, 0.025, respectively), lower risk of acute GVHD (RR = 0.58 for matched, RR = 0.60 for one-antigen mismatched, RR = 0.66 for two-antigen mismatched, P = 0.15, 0.011, 0.003, respectively), and inferior neutrophil recovery (RR = 0.69 for matched, RR = 0.51 for one-antigen mismatched, RR = 0.48 for two-antigen mismatched, P = 0.062, <0.0001, <0.0001, respectively) compared to HLA-DRB1 one-allele mismatched UBMT HLA zero to two antigen mismatched UCBT is a favorable second alternative donor/stem cell source with similar survival outcome with HLA-DRB1 one-allele mismatched UBMT, the current recommended second alternative donor. However, risk of relapse was higher among UCBT, that it should be carefully decided according to disease and clinical status of the recipients.

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FREQUENCY OF CD4$^+$CD25^{HI}FOXP3$^+$ REGULATORY T CELLS HAS DIAGNOSTIC AND PROGNOSTIC VALUE AS A BIOMARKER FOR ACUTE GRAFT-VERSUS-HOST-DISEASE

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Regulatory T cells (Treg) are important for maintaining tolerance after bone marrow transplantation (BMT) in experimental models. However, the relationship between Treg and acute graft-versus-host disease (GVHD) in BMT recipients is not well established. We prospectively analyzed Treg frequency in 215 BMT patients (125 allogeneic, 90 autologous). Fresh blood samples were acquired within 24 hours of GVHD onset and at equivalent time points in patients without GVHD. We measured by flow cytometry the frequency of CD4$^+$CD25^{hi}FOXP3$^+$ cells within total lymphocytes. There were no significant differences between patients with and without GVHD for age, conditioning intensity, and day of sample acquisition. Recipients from unrelated or HLA-mismatched donors were overrepresented in the GVHD group. Autologous (N = 90) and allogeneic BMT patients without GVHD (N = 65) had the same mean Treg frequency (1.09% ±0.10 vs. 1.09% ±0.11, p = 0.54), showing that the use of calcineurin inhibitors may not affect Treg reconstitution. Patients with GVHD (N = 60) had a T reg frequency that was 40% less (0.66% ±0.07, p < 0.001) than those without GVHD. Frequencies of Tregs were significantly reduced in patients with ≥ grade II GVHD at onset compared to patients without GVHD (p < 0.001). The area under the Receiver Operating Characteristic curve for Treg frequency as an independent biomarker of GVHD was 0.69. Treg frequency also correlated with the eventual maximum overall grade of GVHD (r = -0.33; p < 0.001), suggesting prognostic value for this measurement. Therefore, we evaluated whether Treg frequency would correlate with outcomes by dividing the 60 patients with GVHD according to their median Treg frequency (0.5%). Patients with low Treg frequency had a significantly greater non relapse mortality (NRM) (41% vs. 8%, p = 0.03) than patients with high Treg frequency, which resulted in an inferior survival at two years (38% vs. 63%, p = 0.03)(Table 1). GVHD accounted for the majority of NRM in the low Treg frequency group. Relapse mortality was similar between groups (p = 0.9)(Table1). This difference in survival remained significant after adjusting for other important prognostic

Table 1. Clinical outcomes according to CD4$^+$CD25^{hi}FOXP3$^+$ frequency at GVHD onset

	Treg Frequency ≥ 0.5%	Treg Frequency < 0.5%	
Outcome	(N = 30)	(N = 30)	p value
1 yr Non-Relapse Mortality	8% (95% CI, 2-27)	41% (95% CI, 23-61)	0.03
2 yr Relapse Mortality	25% (95% CI, 15-40)	20% (95% CI, 11-35)	0.9
2 yr Overall Survival	63% (95% CI, 43-91)	38% (95% CI, 23-63)	0.03

factors such as age, degree of HLA-match, and conditioning intensity ($p = 0.05$). In this large set, frequency of $CD4^+CD25^{hi}FOXP3^+$ Tregs at onset of GVHD correlates with GVHD severity, eventual maximum GVHD grade and NRM. Treg frequency thus has important diagnostic and prognostic value as a biomarker for acute GVHD.

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A PROSPECTIVE, RANDOMIZED DOUBLE-BLIND PHASE III TRIAL OF APREPITANT VS. PLACEBO PLUS ORAL ONDANSETRON AND DEXAMETHASONE FOR THE PREVENTION OF NAUSEA AND VOMITING (N/V) ASSOCIATED WITH HIGHLY EMETOGENIC PREPARATIVE REGIMENS PRIOR TO HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

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Delayed N/V is often a major toxicity in patients undergoing ablative preparative regimens prior to HSCT. Aprepitant (APR), an NK-1 antagonist is effective in preventing delayed N/V with moderate and highly emetogenic standard dose chemotherapy and thus may be of value in the transplant setting. However APR interacts with cytochrome P450 involved in the bioactivation of high dose cyclophosphamide, and may interfere with etoposide pharmacokinetics; thus may impact regimen related toxicity (RRT) and survival post transplant. While several small Phase II studies have suggested the benefit of APR in HSCT, no prospective comparisons have been reported. We performed a randomized (1:1) blinded Phase III trial to determine the safety and efficacy of APR for N/V due to ablative preparative regimens. Patients received either placebo (PBO) or oral APR 125 mg PO day 1 then 80 mg daily for all days of the preparative regimen and for 3 days after it ended, in addition to oral ondansetron 8 mg PO q 8hrs + IV dexamethasone (DEX) daily during and for 1 day after the preparative regimen. Due to a known drug interaction between APR and dexamethasone, blinded DEX doses were used (10 mg -placebo; 7.5 mg – APR). Patients were stratified based on gender; those with heavy ETOH use were excluded. Clinical evaluations were performed daily with the primary endpoint being a CR, defined as: no emesis and no or mild nausea [less than grade (gr) 3 using CTC 2.0 criteria]. Other endpoints included; major response (MR): 1 episode of emesis or moderate nausea; minor response (mR): 2–4 episodes of emesis; and failure (F): >4 episodes of emesis. Major efficacy (ME) = CR + MR. Nausea was measured on a 100 mm visual analog scale (VAS) with 0 = no nausea. Safety analyses performed included grade 3-5 toxicities, time to engraftment, PFS and OS. The 181 randomized patients were balanced with respect to age, weight, donor source and h/o N/V with prior chemotherapy. Patients received one of 5 ablative prep regimens: CY/TBI/VP16 (36), CY/TBI (79), IV BU/CY (19), PO BU/CY (34), and BCV(16). Two pts never proceeded to transplant so only 179 pts are eligible for analysis. Efficacy: see Table. Days to engraftment; grade 3-5 RRT, PFS and OS were identical between the two groups.

Conclusions: When used up to 10 days with ablative HSCT regimens, aprepitant significantly improved N/V with a major impact on emesis rates. It appears safe for this indication with no impact on WBC and PLT engraftment or PFS/OS.

Ondansetron/dexamethasone +/- Aprepitant for BMT regimen related N/V: Results

	Aprepitant	Placebo	p value
% ptts with no emesis during study period	73.3	22.5	<0.001
% pts with CR: no emesis + < gr 3 nausea during entire period	48.9	14.6	<0.001
% of days no emesis and < gr 3 nasuea, all pts	81.9	65.8	<0.001
Ave VAS scores	16.5	16.9	0.892
Composite MR	16.0	16.9	0.011
Composite mR	2.0	10.3	<0.001
Composite F	0.1	2.2	0.001
Composite ME	97.9	87.4	<0.001